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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,379	11/24/2003	Natalya Rapoport	T5986.PCT.US.B	4634

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EXAMINER	
KARPINSKI, LUKE E	
ART UNIT	PAPER NUMBER
1616	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,379	RAPOPORT, NATALYA	
	Examiner	Art Unit	
	LUKE E. KARPINSKI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *2,4,6,8 and 13-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7,9-12 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/15/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction/Election Requirement

Applicant's election with traverse of Group I (claims 1-12 and 16-20) drawn to a method in the reply filed on 11/19/2007 is acknowledged. The traversal is on the ground(s) that the method cannot be performed with a hydrophobic solvent. Although Applicants argument is found persuasive the restriction requirement still stands on the basis that the composition can be used in a different method. For example the same composition can be used in a method such as a process that utilizes ultrasound at 101 to 150 kilohertz. Thus, the restriction is maintained. Applicant's election with traverse of poly (ethylene oxide) -poly (propylene oxide) -poly (ethylene oxide) as the polymer in the reply filed on 11/19/2007 is also acknowledged. However, Applicant has not provided any specific grounds for traversal; thus the species requirement is also maintained. The requirement is still deemed proper and is therefore made FINAL.

Claims

Claims 1-20 are currently pending.

Claims 2, 4, 6, 8, and 13-17 are withdrawn as non-elected subject matter.

Claims 1, 3, 5, 7, 9-12, and 18-20 are under consideration in this action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. **Claims 1, 3, 5, 7, 9-11, and 18-20 are rejected under 35 U.S.C. 103(a)** as being unpatentable over US Patent No. 5,827,533 to Needham in view of US Patent No. 6,353,055 B1 to Kabanov et al. and US Patent No. 5,830,430 to Unger et al.

Applicant claims a method for delivery of a hydrophobic drug to a selected site comprising administering a composition comprising a micellar drug carrier with a hydrophobic core and a hydrophobic drug, wherein said micelle drug carrier is a member selected from ABA-triblock copolymers or a mixture of said copolymers and Pegylated phospholipids. Said method also comprises applying ultrasound at 20-100

kilohertz to effect drug release form the carrier. The Applicant also claims specific monomers for the polymer and specific drugs.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Needham teaches:

Methods for delivery of a hydrophobic drug (col. 17, lines 3-5; doxorubicin is a hydrophobic drug as taught by the instant specification in claim 11), delivery to a selected site in a patient (col. 21, lines 2-7) comprising: a micellar drug carrier (col. 5, line 66 to col. 6, line 5), a hydrophobic core (col. 9, line 64 to col. 10 , line 6), PEGylated lipids, specifically phosphatidylethanolamine which is a synonym for 1,2-diacyl-sn-glycero-3-phosphoethanolamine (col. 9, lines 26-52), anthracycline (col. 17, line 4), and the use of poly (propylene oxide) –poly (ethylene oxide) diblock copolymers as micelle forming surfactants in combination with the liposome membrane (col. 24, lines 3-13).

Kabanov et al. teach:

ABA triblock copolymers (col. 3, line 18).

That both diblock and tribllock copolymers are useful for delivery of an active to cells (col. 3, lines 26-31).

A triblock copolymer of poly (ethylene oxide) –poly (propylene oxide) –poly (ethylene oxide) hereafter referred to as PEO PPO PEO (col. 11, lines 1-10, structure XIV).

The use of phospholipids within the polymer micelles to increase solubility of the complex and increase biological activity of the compositions (col. 17, lines 20-28).

Unger et al. teach:

Micelle structures for delivery of a bioactive agent (abstract).

The use of ultrasound to effect release of the bioactive agent for cellular uptake at a specified site (col. 27, line 51 to col. 28, line31).

A range of 0.25 to 100 megahertz (col. 28, lines 60-61).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Needham does not teach:

1. The difference between the instant application and that of Needham is that Needham does not expressly disclose a triblock copolymer of PEO PPO PEO. This deficiency in Needham is cured by the teachings of Kabanov.

2. The difference between the instant application and that of Needham is that Needham does not expressly disclose applying ultrasound to release the drug from the carrier. This deficiency in Needham is cured by the teachings of Unger et al.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the triblock copolymer of PEO PPO PEO in the compositions of Needham, as taught by Kabanov et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Needham teaches the use of micelle structures comprising diblock copolymers and Kabanov et al. teach that diblock and triblock copolymers can both be used in the formation of micellar structures. It is common in the art for one of ordinary skill in the art to substitute one functional equivalent for another.

2. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use ultrasound to release the drug from the micelle in the method of Needham as taught by Unger et al. and practice the instant method.

One of ordinary skill in the art would have been motivated to do this because Needham teaches the use of micelle structures to deliver drugs to a selected site in a patient and Unger et al. teach the use of ultrasound to rupture micelle structures and effect delivery of a bioactive agent. Unger et al. teaches that this is useful in delivery and controlled release of a bioactive agent to targeted tissue. The ultrasound can be used to release a desired amount of the bioactive agent to the specific site, while the agent remains within the micelle at other sites in the body, thereby minimizing any negative effects of the agent.

3. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a frequency of 20-100 kilohertz in the method of Needham as taught by Unger et al. and practice the instant method.

One of ordinary skill in the art would have been motivated to do this because Unger et al. teaches using a range of .25 to 100 kilohertz. It was well within the capabilities of one of ordinary skill in the art at the time of the invention to determine an optimum frequency at which the micelles rupture.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus instant claims 1, 3, 5, 7, 9-12, and 18-20 are deemed to be obvious by Needham in view of Kabonov et al. and Unger et al.

2. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,827,533 to Needham in view of US Patent No. 6,353,055 B1 to Kabanov et al. and US Patent No. 5,830,430 to Unger et al. in further view of US Patent No. 4,332,934 to Emanuel et al.

Applicant claims a method for delivery of a hydrophobic drug to a selected site comprising administering a composition comprising a micellar drug carrier with a

hydrophobic core and a hydrophobic drug, wherein said micelle drug carrier is a member selected from ABA-triblock copolymers or a mixture of said copolymers and Pegylated phospholipids. Said method also comprises applying ultrasound at 20-100 kilohertz to effect drug release form the carrier. The Applicant also claims specific monomers for the polymer and specific drugs.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Needham teaches:

The teachings of Needham are set forth above and those teachings are hereby incorporated by reference.

Needham also teaches the use of daunorubicin (col. 17, lines 3-5).

Kabanov et al. teach:

The teachings of Needham are set forth above and those teachings are hereby incorporated by reference.

Unger et al. teach:

The teachings of Needham are set forth above and those teachings are hereby incorporated by reference.

Emanuel et al teach:

Ruboxyl as a less toxic derivative of daunorubicin with higher anti-tumor activity (abstract). It is noted that rubomycin is commonly referred to as daunorubicin (col. 1, lines 23-25).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Needham does not teach:

1. The difference between the instant application and that of Needham is that Needham does not expressly disclose ruboxyl. This deficiency in Needham is cured by the teachings of Emanuel et al.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use ruboxyl in the compositions of Needham, as taught by Emanuel et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Needham teaches the use daunorubicin and Emanuel et al. teach that ruboxyl is a modified daunorubicin that is less toxic and has a higher anti-tumor activity.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus instant claim 12 is deemed to be obvious by Needham in view of Kabonov et al. and Unger et al. in further view of Emanuel et al.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1 and 3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 22 of U.S. Patent No. 6,649,702 to Rapoport et al. in view of Kabanov et al. and Unger et al. as used above.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Rapoport et al claim:

A method for administering a hydrophobic drug to a patient comprising administering block polymer micelles which contain said drug in a hydrophobic core and applying ultrasound to release said drug.

Kabanov et al. teach:

The teachings of Kabanov et al. are set forth above and those teachings are hereby incorporated by reference

Unger et al. teach:

The teachings of Unger et al. are set forth above and those teachings are hereby incorporated by reference

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Rapoport et al. do not claim:

1. The difference between the instant application and that of Rapoport et al. is that Rapoport et al. does not expressly disclose a triblock copolymer. This deficiency in Rapoport et al. is cured by the teachings of Kabanov.

2. The difference between the instant application and that of Rapoport et al. is that Rapoport et al. does not expressly disclose an ultrasound frequency of 20-100 kilohertz to release the drug from the carrier. This deficiency in Rapoport et al. is cured by the teachings of Unger et al.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the triblock copolymer in the compositions of Rapoport et al., as taught by Kabanov et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Rapoport et al. teaches the use of micelle structures comprising block copolymers and Kabanov et al. teach that diblock and triblock copolymers can both be used in the formation of micellar structures. .

2. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a frequency of 20-100 kilohertz in the method of Rapoport et al. as taught by Unger et al. and practice the instant method.

One of ordinary skill in the art would have been motivated to do this because Unger et al. teaches using a range of .25 to 100 kilohertz. It was well within the capabilities of one of ordinary skill in the art at the time of the invention to determine an optimum frequency at which the micelles rupture.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus instant claims 1and 3 are deemed to be obvious type Double Patenting by Rapoport et al in view of Kabonov et al. and Unger et al.

Conclusion

Claims 1, 3, 5, 7, 9-12, and 18-20 are rejected.

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LUKE E. KARPINSKI whose telephone number is (571)270-3501. The examiner can normally be reached on Monday Thursday 9-4 est.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LEK

/Sharmila Gollamudi Landau/
Primary Examiner, Art Unit 1611